Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Prevalence of Culture-Confirmed Tuberculosis Among Patients with Nontuberculous Mycobacterial Disease

Yu He[1], Jun-Li Wang[2], Yan-An Zhang[3,4], Mao-Shui Wang[4–6]

[1]Department of Clinical Laboratory, First Affiliated Hospital of Guangxi Medical University, Nanning, 530021, People's Republic of China; [2]Department of Laboratory Medicine, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, People's Republic of China; [3]Department of Cardiovascular Surgery, Shandong Public Health Clinical Center, Cheeloo College of Medicine, Shandong University, Jinan, 250013, People's Republic of China; [4]Shandong Key Laboratory of Infectious Respiratory Disease, Jinan, Shandong, People's Republic of China; [5]Department of Laboratory Medicine, Shandong Provincial Chest Hospital, Cheeloo College of Medicine, Shandong University, Jinan, 250013, People's Republic of China; [6]Department of Lab Medicine, Shandong Public Health Clinical Center, Cheeloo College of Medicine, Shandong University, Jinan, 250013, People's Republic of China

Correspondence: Yan-An Zhang, Department of Cardiovascular Surgery, Shandong Public Health Clinical Center, 46# Lishan Road, Jinan, 250013, People's Republic of China, Email zhangtbgroup@163.com; Mao-Shui Wang, Department of Laboratory Medicine, Shandong Public Health Clinical Center, 46# Lishan Road, Jinan, 250013, People's Republic of China, Email wangmaoshui@gmail.com

Background: Currently, the prevalence of nontuberculous mycobacteria (NTM) strains isolated from mycobacterial cultures has been well characterized. However, the data on the prevalence of tuberculosis (TB) in patients with NTM disease remain unclear.

Methods: Between January 2012 and August 2020, consecutive patients with positive mycobacterial cultures were included for analysis. The identification of *Mycobacteria* spp. was performed using the DNA array method or sequencing of 16S rDNA. NTM disease is diagnosed when the same infectious agent is identified in at least two sputum or is identified in sterile samples.

Results: A total of 997 strains were isolated from 828 inpatients. Of them, 261 inpatients (31.5%) were diagnosed as NTM disease. The mean age of the 261 patients was 55.7 ±15.5 years old and 64.0% (n = 167) of them were male. The prevalence of culture-confirmed TB patients among patients with NTM disease was estimated as 8.0% (21/261).

Conclusion: TB is common in NTM disease and caution should be taken when initiating the treatment of NTM disease.

Keywords: prevalence, tuberculosis, culture, nontuberculous mycobacteria, diagnosis

Introduction

Nontuberculous mycobacteria (NTM) are emerging opportunistic pathogens of humans. Although a revised guideline has been issued recently, the treatment of NTM disease (NTM-D) remains a challenge.[1] First, NTM infections usually share some symptoms with tuberculosis (TB) and the discrimination between them remains relying on microbiological evidence. Second, most NTM species are resistant to first-line anti-TB agents,[2] and treatment choices for NTM diseases were largely based on experience and not scientifically based evidence. Third, the identification of NTM is not routinely performed in most areas, and this makes a significant delay in the diagnosis[3] and poor outcomes are then easily to occur. In addition, a previous study suggests that the prevalence of NTM infection shows an increasing trend during the last decades,[4] and this makes the management of NTM disease more complicated.

In a previous study, we found that a significant proportion (53.4%) of NTM diseases were T-SPOT.TB positive in China, and the positive rate was higher than that of healthcare workers (13.9%).[5,6] This finding demonstrated that *Mycobacterium tuberculosis (M.TB)* infections are common in patients with NTM disease. Currently, the prevalence of NTM strains isolated from mycobacterial cultures has been well characterized, and the rate varies widely, reported from 1% to 8% between studies.[2,4,7–9] However, the data on the prevalence of TB in patients with NTM disease remain

Received: 23 February 2022
Accepted: 9 June 2022
Published: 17 June 2022

unclear. Therefore, this retrospective study was conducted to evaluate the prevalence of co-infection of TB and NTM diseases, this would be helpful to tailor the diagnosis and management of NTM disease.

Methods

This study was conducted at the Shandong Provincial Chest Hospital and confronted with the Helsinki Declaration. The study protocol was approved by the Ethical Committee of Shandong Provincial Chest Hospital (NO. 2020XKYYEC-29). Because of a retrospective design and anonymous analysis employed in the study, written informed consent was waived by the Ethical Committee of Shandong Provincial Chest Hospital.

Between May 2012 to June 2021, consecutive patients who were positive for mycobacterial cultures during the same episode of illness were included for analysis. Mycobacterial culture was performed using Löwenstein-Jensen medium method and quality control was conducted as previously reported.[2] NTM was initially screened for resistance to p-nitrobenzoic acid. Then, NTM species were further identified by 1) 16S rRNA gene sequence analysis (MicroSeq ID Microbial Identification Software, version 2.0; Applied Biosystems, Foster City, CA, USA),[10] or 2) DNA microarray chip method using Mycobacteria Identification Array Kit (CapitalBio, Beijing, China).[11] According to the microbiological criteria established by the ATS/ERS/ESCMID/IDSA, NTM disease is diagnosed when the same infectious agent is identified in at least two sputum (or one sputum and one stool) or is identified in sterile samples, such as tissues, bronchial brushing, and BALF (bronchial alveolar lavage fluid).[1,12] Continuous data were presented as mean ± standard deviation (SD) and categorical data were presented as count (percentages).

Results

In the period from May 2012 to June 2021, 25,617 mycobacterial strains were found in clinical samples. Of them, 1107 (4.3%) strains were identified as NTM species, including 110 strains isolated from outpatients and 997 strains from 828 inpatients (Table 1). The mean age of the 828 patients was 55.8 ±16.0 years and 64.4% (n=533) of them were male. Among them, TB isolates were cultured from 85 patients (10.3%).

Fourteen patients (1.7%) were culture-positive with at least one strain, and two of them were diagnosed as NTM disease, this was because one strain isolated from a sterile sample (Patient 1) and the same strain isolated from four separate sputum (Patient 2). In addition, the same strains were isolated from at least two sputum in 145 patients (17.5%), at least one sputum and one sterile sample in 49 patients (5.9%), at least one sputum and one stool in 4 patients (0.5%), or at least one sterile sample in 61 patients (7.4%). The remaining 555 patients were all single positive for NTM isolates, which has been further identified. Finally, a total of 261 inpatients (31.5%) were diagnosed as NTM disease and included for further analysis.

The mean age of the 261 patients was 55.7 ±15.5 years old and 64.0% (n=167) of them were male. The corresponding 261 strains included *M. intracellulare* (n=195, 74.7%), *M. kansasii* (n=25, 9.6%), *M. chelonei* (n=21, 8.0%), *M. fortuitum* (n=8, 3.1%), *M. avium* (n=7, 2.7%), and others (n=5, 1.9%). Among the 261 patients, TB isolates were cultured from 21 patients (8.0%), and cough (n=215, 82.4%) was the most common symptoms, followed by fever (n=107, 41.0%), chest tightness (n=78, 29.9%), shortness of breath (n=80, 30.7%), hemoptysis (n=41, 15.7%), chest pain (n=19, 7.3%), and fatigue (n=11, 4.2%). In addition, the most common radiological findings were as follows: pulmonary involvement (n=21, 100.0%), pleural involvement (n=3, 14.3%), lymph node (n=1, 4.8%), and chest wall involvement (n=1, 4.8%).

Discussion

In this laboratory-based retrospective cohort study, we found that the prevalence of confirmed TB in patients with positive NTM culture was 10.3% and the prevalence in patients with confirmed NTM disease was 8.0%. The prevalence of confirmed TB in patients with NTM diseases was high and should not be ignored. Remarkably, this dilemma would lead to a significant misdiagnosis and inappropriate treatment.

The NTM species are distributed dependent on geographical regions and the epidemiology of the NTM infections varied between studies.[13] Similarly, the prevalence of confirmed TB among NTM diseases also has such characteristics. In a Korean study, Lin et al found that the proportion of NTM-TB co-infection among patients with NTM infection was 19.3% (87/450).[14] In Beijing, Zhao et al found that, of the 102 patients with positive mycobacterial

Table 1 The Patient Characteristics and Distribution of NTM Species in the Study

	NTM Culture (+, n)	NTM Disease (n)
N	828	261
Age (years)	55.8 ±16.0	55.7 ±15.5
Sex, male	533 (64.4%)	167 (64.0%)
TB culture (+)	85 (10.3%)	21 (8.0%)
First-line drug resistance (TB)	n=37	n=10
Isoniazid	9 (24.3%)	4 (40.0%)
Rifampicin	6 (16.2%)	2 (20.0%)
Streptomycin	5 (13.5%)	2 (20.0%)
Ethambutol	2 (5.4%)	1 (10.0%)
MDR-TB	4 (10.8%)	1 (10.0%)
Symptoms		
Cough	621 (75.0%)	215 (82.4%)
Fever	316 (38.2%)	107 (41.0%)
Chest tightness	239 (28.9%)	78 (29.9%)
Shortness of breath	232 (28.0%)	80 (30.7%)
Hemoptysis	108 (13.0%)	41 (15.7%)
Chest pain	68 (8.2%)	19 (7.3%)
Fatigue	36 (4.3%)	11 (4.2%)
Radiological findings	n=85	n=21
Pulmonary TB	83 (97.6%, 83/85)	21 (100.0%, 21/21)
Pleural TB	13 (15.3%, 13/85)	3 (14.3%, 3/21)
Lymph node TB	10 (11.8%, 10/85)	1 (4.8%, 1/21)
Chest wall TB	3 (3.5%, 3/85)	1 (4.8%, 1/21)
Osseous TB	1 (1.1%, 1/85)	
NTM species	n=997	n=261
M. intracellulare	662 (66.4%, 662/997)	195 (74.7%, 195/261)
M. kansasii	111 (11.1%, 111 /997)	25 (9.6%, 25/261)
M. chelonei	103 (10.3%, 103/997)	21 (8.0%, 21/261)
M. fortuitum	39 (3.9%, 39/997)	8 (3.1%, 8/261)
M. gordonae	20 (2.0%, 20/997)	2 (0.8%, 2/261)
M. avium	20 (2.0%, 20/997)	7 (2.7%, 7/261)
Others	42 (4.2%, 42/997)	3 (1.1%, 3/261)

Abbreviations: NTM, nontuberculous mycobacteria; TB, tuberculosis; MDR, multiple drug resistance.

culture, 84 have *M.TB*, 16 have NTM, and 2 have both *M.TB* and NTM. Therefore, the prevalence of confirmed TB in patients with positive NTM culture was calculated as 11.1% (2/18). In Africa, Bonnet et al found that, among the 128 patients with NTM isolates, four patients were also *M.TB* culture-positive.[15] It was then the estimated prevalence was calculated as 3.1% (4/128). However, very few patients (n=12) of them met the ATS criteria for NTM disease. In our study, the prevalence of confirmed TB in NTM patients with bacterial evidence was 8.0%. However, the actual prevalence would be even higher. This is because only a part of TB patients were culture-positive.[16] According to my experience, the prevalence is estimated to reach about 15%. In general, this co-infection phenomenon is usually neglected in clinical practice and most co-infections are reported as case reports, such as Yılmaz et al,[17] Sharma et al,[18] Izadi et al.[19]

Treatment of NTM disease is difficult due to the uncertainty regarding when treatment should be started and which regimen is most likely to achieve successful treatment.[1] There is no known treatment for many NTM infections. The initiation of NTM treatment should be individualized considering disease types, comorbid conditions, and age.[17] Usually, NTM isolates were resistant to first-line anti-TB drugs.[4] Therefore, these drugs would not be the first choice for the treatment of patients with NTM disease. However, since co-infection exists, these drugs sensitive for TB but resistant to

NTM stains should be reconsidered. Moreover, an misdiagnosis of NTM disease can be made due to the presence of TB isolates. Fortunately, in the study, *M. intracellulare* was the most common strain isolated from clinical samples, whose treatment has been well characterized.[20,21]

Previously, risk factors of NTM or TB infection have been investigated. However, the risk factors of TB co-infection among NTM diseases remain unclear. Remarkably, the two infections usually share some risk factors, such as HIV, chronic respiratory disease, corticosteroid use, and anti–TNF-α therapy.[22–24] To appreciate the risk factors of TB would be helpful to improve the management of NTM disease, especially facilitating early diagnosis of co-infection. Besides, TB, or NTM? Which one is the first infection? The question is also essential and useful to answer the potential mechanism involving the co-infection. In a previous study, it was found that previous TB is a major risk factor for NTM pulmonary disease.[25] Similarly, in patients with previous NTM disease, the risk of TB was also increased.[26] Therefore, the condition of NTM or TB infection may facilitate the infection process of each other. In a word, further study should be performed to investigate the risk factors of TB among NTM diseases, the work may be helpful to resolve this dilemma of management of NTM disease.

Although some interesting findings were observed, the study also has some limitations. First, due to the overlap of clinical and radiological findings between TB and NTM diseases, a culture method was used for TB diagnosis, this would decrease the actual prevalence of TB infection among NTM diseases. Therefore, tools that can simultaneously and accurately diagnose TB and NTM disease are urgently needed. Second, NTM recovery on solid culture is limited, the burden may also be underestimated. Third, due to limited information, the role of IGRA in preventive therapy has not been evaluated in patients with NTM disease. In my opinion, this adjunctive therapy targeting TB should be taken into account, especially when a true positive IGRA result occurs (excluding the influence of NTM antigens, such as ESAT-6, CFP10, or both). Third, due to a significant NTM and TB co-infection, caution should be taken when the treatment of NTM disease is initiated.

In conclusion, TB is common in NTM disease and caution should be taken when initiating the treatment of NTM disease.

Data Sharing Statement

The data and code for this study can be requested from the corresponding author (Mao-Shui Wang).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Science Research and Technology Development Plan of Baise City (20203405), and the Development and Application Project for Medical Appropriate Technology of Guangxi (S2020035).

Disclosure

The authors have no competing interests in this work.

References

1. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. *Eur Respir J*. 2020;56(1):2000535. doi:10.1183/13993003.00535-2020
2. Jing H, Wang H, Wang Y, et al. Prevalence of nontuberculous mycobacteria infection, China, 2004–2009. *Emerg Infect Dis*. 2012;18(3):527–528. doi:10.3201/eid1803.110175
3. Jing H, Tan W, Deng Y, et al. Diagnostic delay of pulmonary nontuberculous mycobacterial infection in China. *Multidiscip Respir Med*. 2014;9(1):48. doi:10.1186/2049-6958-9-48

4. Xu D, Han C, Wang MS, Wang JL. Increasing prevalence of non-tuberculous mycobacterial infection from 2004–2009 to 2012–2017: a laboratory-based surveillance in China. *J Infect*. 2018;76(4):422–424. doi:10.1016/j.jinf.2017.12.007
5. Wang MS, Wang JL, Wang XF. The performance of interferon-gamma release assay in nontuberculous mycobacterial diseases: a retrospective study in China. *BMC Pulm Med*. 2016;16(1):163. doi:10.1186/s12890-016-0320-3
6. Deng Y, Li Y, Wang F, et al. Tuberculosis prevention in healthcare workers in China 10 years after the severe acute respiratory syndrome pandemic. *ERJ Open Res*. 2015;1(1):00015–2015. doi:10.1183/23120541.00015-2015
7. Mbeha B, Mine M, Motswaledi MS, Dewar J. Nontuberculous Mycobacteria, Botswana, 2011–2014. *Emerg Infect Dis*. 2019;25(7):1401–1403. doi:10.3201/eid2507.181440
8. Chunfang W, Jihong R, Yu W, et al. Prevalence of nontuberculous mycobacterial disease in the Changchun District of China. *Curr Microbiol*. 2021;78(4):1643–1647. doi:10.1007/s00284-021-02422-y
9. Tan Y, Deng Y, Yan X, et al. Nontuberculous mycobacterial pulmonary disease and associated risk factors in China: a prospective surveillance study. *J Infect*. 2021;83(1):46–53. doi:10.1016/j.jinf.2021.05.019
10. El Amin NM, Hanson HS, Pettersson B, Petrini B, Von Stedingk LV. Identification of non-tuberculous mycobacteria: 16S rRNA gene sequence analysis vs. conventional methods. *Scand J Infect Dis*. 2000;32(1):47–50. doi:10.1080/00365540050164218
11. Huang JJ, Li YX, Zhao Y, et al. Prevalence of nontuberculous mycobacteria in a tertiary hospital in Beijing, China, January 2013 to December 2018. *BMC Microbiol*. 2020;20(1):158. doi:10.1186/s12866-020-01840-5
12. He Y, Zhang YA, Wang MS. Stool culture for diagnosis of nontuberculous mycobacteria pulmonary disease: an indirect evidence. *J Infect*. 2021;83:607–635. doi:10.1016/j.jinf.2021.08.002
13. Varghese B, Al-Hajoj S. A global update on rare non-tuberculous mycobacteria in humans: epidemiology and emergence. *Int J Tuberc Lung Dis*. 2020;24(2):214–223. doi:10.5588/ijtld.19.0194
14. Lin CK, Yang YH, Lu ML, et al. Incidence of nontuberculous mycobacterial disease and coinfection with tuberculosis in a tuberculosis-endemic region: a population-based retrospective cohort study. *Medicine*. 2020;99(52):e23775. doi:10.1097/MD.0000000000023775
15. Bonnet M, San KC, Pho Y, et al. Nontuberculous mycobacteria infections at a provincial reference hospital. *Cambodia Emerg Infect Dis*. 2017;23(7):1139–1147. doi:10.3201/eid2307.170060
16. Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990–2010; a longitudinal analysis of national survey data. *Lancet*. 2014;383(9934):2057–2064. doi:10.1016/S0140-6736(13)62639-2
17. Yilmaz N, Ucar EY, Saglam L. Mycobacterium tuberculosis and nontuberculous mycobacteria coinfection of the lungs. *Turk Thorac J*. 2017;18(1):23–26. doi:10.5152/TurkThoracJ.2017.16034
18. Sharma K, Gautam N, Sharma M, et al. Ocular mycobacteriosis-dual infection of M. tuberculosis complex with M. fortuitum and M. bovis. *J Ophthalmic Inflamm Infect*. 2017;7(1):2. doi:10.1186/s12348-016-0121-0
19. Izadi N, Derakhshan M, Samiei A, Ghazvini K. Co-infection of long-standing extensively drug-resistant Mycobacterium tuberculosis (XDR-TB) and non-tuberculosis mycobacteria: a case report. *Respir Med Case Rep*. 2015;15:12–13. doi:10.1016/j.rmcr.2014.11.006
20. Wallace RJ, Brown BA, Griffith DE, et al. Initial clarithromycin monotherapy for Mycobacterium avium-intracellulare complex lung disease. *Am J Respir Crit Care Med*. 1994;149(5):1335–1341. doi:10.1164/ajrccm.149.5.8173775
21. Griffith DE, Eagle G, Thomson R, et al. Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by mycobacterium avium complex (CONVERT). A prospective, open-label, randomized study. *Am J Respir Crit Care Med*. 2018;198(12):1559–1569. doi:10.1164/rccm.201807-1318OC
22. Lan R, Yang C, Lan L, et al. Mycobacterium tuberculosis and non-tuberculous mycobacteria isolates from HIV-infected patients in Guangxi, China. *Int J Tuberc Lung Dis*. 2011;15(12):1669–1675. doi:10.5588/ijtld.11.0036
23. Andrejak C, Nielsen R, Thomsen VO, Duhaut P, Sorensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax*. 2013;68(3):256–262. doi:10.1136/thoraxjnl-2012-201772
24. Winthrop KL, Chang E, Yamashita S, Iademarco MF, LoBue PA. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. *Emerg Infect Dis*. 2009;15(10):1556–1561. doi:10.3201/eid1510.090310
25. Fusco da Costa AR, Falkinham JO, Lopes ML, et al. Occurrence of nontuberculous mycobacterial pulmonary infection in an endemic area of tuberculosis. *PLoS Negl Trop Dis*. 2013;7(7):e2340. doi:10.1371/journal.pntd.0002340
26. Hsing SC, Weng SF, Cheng KC, et al. Increased risk of pulmonary tuberculosis in patients with previous non-tuberculous mycobacterial disease. *Int J Tuberc Lung Dis*. 2013;17(7):928–933. doi:10.5588/ijtld.12.0675